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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,428	VLODAVSKY ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,41,42,45,46,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,41,42,45,46,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-28-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 28, 2005 has been entered. Claims 38, 41, 42, 45, 46, 48 and 49 are pending and under examination.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on November 28, has been considered by the examiner. See signed and attached PTO-1449.

Withdrawn Rejections/Objections

2. Any objection or rejection not expressly reiterated in the Maintained Rejections section below is hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112 – 1st Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement:

4. Claims 42-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of treating a subject by inhibiting heparanase glycosidase activity by administering an effective amount of any one of eosinophil secondary granules protein, which includes major basic protein (MBP). It is well documented and known in the art that eosinophils are cytotoxic. For example, Furuta et al. describe eosinophils as such: "Eosinophils normally reside in tissues with mucosal surfaces such as the gastrointestinal tract. A variety of inflammatory and allergic diseases, including inflammatory bowel disease (IBD), parasitic infections, eosinophilic gastroenteritis, asthma, atopic dermatitis, and allergic rhinitis are associated with increases in the number of eosinophils within affected tissues". Thus how the administration of cytotoxic proteins to a subject and which will not elicit an inflammatory immune system response while still functioning to inhibit heparanase glycosidase activity is unclear because the concentration necessary for inhibition of a heparanase glycosidase activity may exceed the lowest levels of detection in the subject.

The factors to be considered in determining whether undue experimentation is required are summarized above in paragraph 8. The quantity of testing in order to

determine if administration of a pharmaceutical composition that comprises, for example MBP, and whether or not the concentration that is administered to a subject not only inhibits heparanase activity but also elicits an adverse and negative immune response in the patient is considerable because the use of this protein for this heparanase effect has never been considered in the prior art. The only examples in the prior art are drawn to methods of inhibiting eosinophils and the immune response that they cause, and not to administering them to a subject. The specification does not even address this issue what so ever so there is zero guidance in how a skilled artisan should have to deal with such a situation. The only working example present is drawn to administration of MBP in a mice, but again it is not addressed what the appropriate protocol might be to avoid an adverse immune response. Further, it seems that no testing was done on this matter in the mice which were administered MBP. The nature of the invention is such that it may put subjects at risk for adverse immune responses which may be lethal to some. The relative skill of those in the art is exceedingly high and the predictability of whether the administration of the composition will adversely affect the subjects due to an inflammatory immune response is huge.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 38 and 41 are rejected under 35 U.S.C. 102(a) as being anticipated by Davis et al. Davis et al. teach pharmaceutical compositions of MBP, EPO, EDN and ECP in PBS (a pharmaceutically acceptable buffer, or diluent) at concentrations of 0.001 μmol/L to 50 μmol/L (p. 989, 2nd column, 1st paragraph).

Response to Arguments

7. The Examiner acknowledges and appreciates the amendment to the claims that more distinctly define the invention. Specifically, the recitation of which MBP that it intended for use in the claimed invention as well as including administration of a therapeutically effective amount.

35 U.S.C 112

Enablement:

The new enablement rejections of the previous Office action, sections 15 and 16, from May 27, 2005 are withdrawn. Applicants arguments and the amendments to the claims are persuasive to overcome the rejections. However Applicant's arguments concerning the remaining enablement rejection of claims 42-45, section 10 of the previous Office action, have been fully considered but they are not persuasive at this time.

The issue at point is the administration of toxic proteins to patients in need thereof that will inhibit heparanase glycosidase catalytic activity in a amount that is

effective to do so, but which will not introduce an immune response to said patient. Applicants assert the following on p. the Remarks (last paragraph): "There are no reports to date that MBP may be toxic, except for only one report, where MBP was administered directly to guinea pig bronchi." That report is used as evidence by Applicant that the administration of MBP was 100-1000 times higher than the present study. However, the examiner does not find this reasoning and statement persuasive because for instance, Kleine et al. (Am J Physiol. 1998 Jul; 275(1 Pt 1):C93-103) it is stated in the introduction, p.C93, 1st paragraph: "Purified MBP is toxic to a number of cells types, including parasites, tumor cells, a variety of mammalian cells such as splenic, intestinal, and endothelial cells, and airway epithelium." In this sentence/statement alone (emphasis added) Kleine et al. cite ***11*** different prior art references. Thus Applicants assertion that there are no reports but one that suggest that MBP is toxic is contrary to the prior art teachings. The rest of the paragraph reads as such: "The cytotoxic effect of MBP is believed to be important for immunity, by killing pathogens, and in disease processes associated with eosinophil infiltration and degranulation. For example, MBP has been measured has been measured in inflammatory lesions in tissues including cornea, liver, and intestine. Furthermore, elevated MBP levels have been measure in the sputum of patients with asthma, and a considerable body of evidence suggests that MBP mediates the tissue damages associated in asthma." Thus the prior art does suggest that MBP is indeed toxic. Applicants argue that a number of anti-cancer treatments are highly toxic, even at therapuetic dosages. The examiner agrees with this point. However, it took some

considerable bodies of evidence and concrete disclosure to conclude that these chemotherapeutics (as an example) were indeed enabled. Applicant has stated that they would be willing to submit a declaration which presents their unpublished data which shows that mice treated with MBP were viable and that they had no adverse or negative immune response, it is deemed that this sort of declaration would facilitate prosecution of this case.

102(a)

8. The rejection of claims Davis et al. from the previous Office action maintained because the amendment of claim 38 to include only MBP does not over come the teachings of Davis et al. because on p. 989, 2nd column, 1st paragraph, it is taught that 50 μl of *each* granule protein (meaning MBP, EDN, ECP and EPO) at 0.001 μmol/L to 50 μmol/L was diluted in sterile PBS and the composition injected into waste skin. After 15-30 minutes, injection *sites* were biopsied. It is the examiners interpretation of this prior art reference that each individual eosinophil granule protein was independently formulated and independently injected, and thus MBP was used alone. Thus the teachings anticipate the limitations of the claims.

New Rejections/Objections

Claim Objections

9. Claims 42, 46 and 49 objected to because of the following informalities: The phrase "....which is the 117 amino acid residue of MBP....." would be clearer if "of" were removed from the phrase. Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

11. Claims 41, 45 and 48 recites the limitation "The method according to claim 46, wherein the eosinophil secondary granules basic protein is provided as one of a purified recombinant protein, a fusion protein, a cell, a cell line, a tissue endogenously expressing said protein and a lysate thereof". There is insufficient antecedent basis for this limitation in the claim because the claims they depend from (e.g. claims 38, 42 and 46) are drawn strictly to the 117 amino acid major basic protein. Thus

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled** to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 38, 41, 46 and 48 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kleine et al. (Am J Physiol. 1998 Jul; 275(1 Pt 1):C93-103).

The claims are drawn to a composition for the inhibition of heparanase glycosidase where the composition consists essentially of two components: component one is a pharmaceutically acceptable material chosen from a carrier, diluent, excipient or an additive and component two is the 117 amino acid major basic protein (MBP) at a concentration of 1-180 μg/ml.

Kleine et al. teach the purification of the 117 amino acid major basic protein in a buffer of 150 mM NaCl and 25 mM acetate buffer at pH 4.3 at a concentration of 1.4 mg/ml (10^{-4}M). In Fig. 3 a concentration upto 400nM is used which is equal to 9.6 μg/ml. Thus this is essentially component two. The purified MBP is then added to another solution known as Ringer's solution (Ringer's solution is known in the prior art as an aqueous solution of chlorides of sodium, potassium, and calcium that is isotonic to animal tissue and is used topically as a physiological saline and, in experiments, to bathe animal tissues.). Thus this is component one.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SMN
23 December 2005

JON WEBER
SUPERVISORY PATENT EXAMINER